Postmenopausal Pellet vs. FDA approved Hormonal Therapy: An Assessment of Serum Estradiol and Testosterone Levels

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BACKGROUND

• Hormone therapy (HT) refers to the use of either synthetic or animal derived estrogen or combination estrogen/progesterone for prevention or treatment of diseases.
• It was approved by FDA to treat menopausal symptoms.
• It was widely used through 1990s, but use fell dramatically after the publication of the initial safety results from the Women's Health Initiative (WHI) trials in 2002.
• A gap between the need of treatment for menopausal symptoms and public concern over the safety of HT explained the fact that many women seek a “safer” alternative treatment options – custom-compounded bioidentical hormone therapy (CBHT).
• CBHT has been marketed as more natural and safer, although it has not been FDA-approved and regulated, the scientific evidence supporting those claims is lacking.

• Several marketed compounded CBH products:
  - Tri-estrogen (tri-est): mixture of 80% estriol, 10% estrone, and 10% estradiol
  - Bi-estrogen (bi-est): mixture of estriol and estradiol in a ratio of 8:1 or 9:1
  - Testosterone and DHEA

• Testosterone may be the primary reason why women want to stick to CBHT.
• There is no proof that CBHT have fewer side effects or are more effective than FDA-approved products. In fact, many FDA-approved products are bioidentical.

• Pellet Hormone therapy (PHT) is a percutaneous form of CBHT with effects lasting 3-6 months.

• Our team have presented safety results of PHT in the 2017 & 2018 NAMS meetings, which showed a significantly higher rates of side effects (mood swing, anxiety, breast tenderness, change in hair pattern, acne, weight gain), AUB and subsequent hysterectomy in PHT. This was despite progesterone supplementation.
OBJECTIVE

• Due to lack of regulation and monitoring, possible overdosage or underdosage, and variable bioavailability of compounded hormones, laboratory monitoring become critical for women on long-term CBHT.

• The objective of the study was to assess the serum estradiol (E2) and total testosterone (T) levels in postmenopausal women treated with PHT and FHT.
METHODS

• Retrospective cohort study (PHT vs FHT)
• 539 postmenopausal women with menopausal symptoms identified from Reading Hospital EMR system
  • 384 women on PHT (estradiol [E2, 6-37.5mg] and/or testosterone [T,12-137.5 mg] pellets)
  • 155 women on FHT
• Serum E2 and T levels, treatment duration, and the number of lab follow-up were extracted from medical records.
RESULTS

• Women on PHT were significantly younger than those in FHT, with mean age (SD) of 51.04 (7.52) and 60.61 (9.56) years (p<.001).

• Women on PHT had significantly longer treatment duration in years than those on FHT (mean [SD]: 3.92 [2.34] vs. 3.33[4.64], p<0.0001).

• Of 384 women on PHT, 373 (97.1%) had serum E2 and T monitored at least once, with mean (SD) total number of E2 and T follow-up of 6.81 (4.57) and 4.98 (3.52), respectively.

• Of 155 women on FHT, 33 (21.2%) had serum E2 and T monitored at least once, with mean (SD) number of E2 and T follow-up of 0.39 (0.86) and 0.14 (0.49), respectively.
• Mean (SD, Min-Max) highest E2 (pg/mL) was significantly higher in PHT group than those in FHT (237.70 [168.55, 10-1 111] vs. 93.45 [130.77, 5.5-465.8], P<0.00001).

• Mean (SD, Min-Max) highest T (ng/dL) was significantly higher in PHT group than those in FHT (192.84 [82.31, 4.3-475] vs. 15.59 [19.52, 0.2-70], P<0.00001).

• Of those on PHT, 4 women had E2 level > 1000 pg/mL and 9 women with T level > 400 ng/dL.
# TABLE 1. COMPARISON OF SERUM E2 AND T LEVEL BETWEEN PHT AND FHT COHORTS

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>P value*</th>
<th>Postmenopausal Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PHT (n=384)</td>
<td>FHT (n=155)</td>
<td></td>
</tr>
<tr>
<td>HT Duration (years)</td>
<td>3.92 (2.34)</td>
<td>3.33 (4.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lowest E2 (pg/mL)</td>
<td>59.97 (42.07)</td>
<td>40.93 (60.40)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Highest E2 (pg/mL)</td>
<td>237.70 (168.55)</td>
<td>93.45 (130.77)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Lowest T (ng/dL)</td>
<td>66.91 (50.4)</td>
<td>12.37 (21.18)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Highest T (ng/dL)</td>
<td>192.84 (82.31)</td>
<td>15.59 (19.52)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td># of Lab F/U for E2</td>
<td>6.81 (4.57)</td>
<td>0.39 (0.86)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td># of Lab F/U for T</td>
<td>4.98 (3.52)</td>
<td>0.14 (0.49)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

* P values were calculated by Mann Whitney U test based on mean (SD) comparison.
### TABLE 2. COMPARISON OF SIDE EFFECT FREQUENCY BETWEEN PHT AND FHT COHORTS

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>PHT (n=384)</th>
<th>FHT (n=155)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>193 (50.3%)</td>
<td>23 (14.8%)</td>
<td>&lt;0.00001*</td>
</tr>
<tr>
<td>Mood swing</td>
<td>37 (9.6%)</td>
<td>4 (2.6%)</td>
<td>0.0052*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>78 (20.3%)</td>
<td>19 (12.3%)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>40 (10.4%)</td>
<td>5 (3.2%)</td>
<td>0.0063*</td>
</tr>
<tr>
<td>Hair pattern change</td>
<td>52 (13.5%)</td>
<td>5 (3.2%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Acne</td>
<td>34 (8.9%)</td>
<td>2 (1.3%)</td>
<td>0.0015*</td>
</tr>
<tr>
<td>Weight gain</td>
<td>136 (35.4%)</td>
<td>8 (5.1%)</td>
<td>&lt;0.00001*</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>57 (16.9%)</td>
<td>25 (20%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Dyslipidemia†</td>
<td>42 (12.3%)</td>
<td>29 (25%)</td>
<td>0.0011*</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>14 (3.7%)</td>
<td>9 (6.2%)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

†Newly onset cases after HT; prior history not included
DISCUSSION

• Recent prescription rates for custom-compounded pellet HT now approach those of FDA-approved hormone prescriptions

• 28-68% of women on HRT are on pellet HT, 86% of women are unaware that it is not FDA approved

• Individualized options for hormone therapy are available to women using FDA-approved options with many dosages/delivery options available

• CBHT may be an option for patients who cannot tolerate other forms of FDA-approved medication (ie. allergies)
DISCUSSION

• Compared to women on FHT, women on PHT had a significantly higher levels of peak E2 and T during treatment

• Most women have E2 and T tested when on PHT but frequency of lab monitoring was lower than expected

• Women on PHT had significantly more side effects overall when compared to women on FHT
LIMITATIONS OF THE STUDY

• Short duration
• Retrospective nature of the study
• Single site
• Unable to assess serum E2 and T responses to dose adjustment
• Unable to assess symptoms improvement after dose adjustment
• Unable to accurately correlate abnormal lab with side effects
CONCLUSION

• When compared with women on FDA-HT, women on PHT had a significantly higher and abnormal level of peak E2 and T during the treatment.

• Although most women had E2 and T tested when they were on PHT, the frequency of laboratory monitoring was still lower than expected.

• Future prospective studies are needed to help develop a clinical guideline for safety monitoring in women on CBHT.
REFERENCES


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